

Topical ciclosporin in the treatment of vernal keratoconjunctivitis in Rwanda, Central Africa: a prospective, randomised, double-masked, controlled clinical trial

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ABSTRACT

Aim To compare the short-term efficiency and safety of topical ciclosporin A (CsA) 2% with dexamethasone 0.1% in the treatment of predominantly limbal vernal keratoconjunctivitis (VKC) in Rwanda, Central Africa.

Methods Consecutive patients with VKC were randomised in a prospective, double-masked, clinical trial to receive either topical CsA 2% dissolved in olive oil vehicle or dexamethasone 0.1% drops for 4 weeks. Both groups then received sodium chromoglycate 2% drops for maintenance therapy for a further 4 weeks. The primary outcome was the reduction in composite score for VKC-related symptoms and signs at 4 weeks. Secondary outcomes included side effects, best-corrected visual acuity, comfort rating of the trial drops during 4 weeks' test medication and relapse rate thereafter.

Results The 366 participants recruited had the limbal (91.5%) or mixed form of VKC. At the end of the 4-week treatment period, the composite score had decreased significantly ($p<0.001$) from baseline without any significant difference between CsA and dexamethasone ($p=0.20$). There were no severe adverse reactions, but CsA drops caused more stinging than the oil placebo and dexamethasone ($p<0.001$). In both treatment groups, the visual acuity had improved at 4 weeks compared with baseline ($p<0.001$) with no significant difference between the treatment arms. The relapse rate following cessation of the trial treatments was similar ($p=0.84$) in both groups.

Conclusion There is no significant difference between the efficiency of topical CsA 2% and dexamethasone 0.1% for the management of acute VKC in Central Africa, but tolerance needs to be improved.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a bilateral chronic allergic inflammation of the external eye. It predominantly affects the conjunctiva over the upper tarsal plate and/or limbus.¹ Limbal VKC is more common in hot, dry environments, and it is an important reason for hospital attendance in eye clinics in Africa, Asia and the Middle East, representing up to 30% of referral among children and adolescents.^{1–3} The intense itching, tearing, mucous stringy discharge and severe photophobia associated with VKC can cause significant morbidity and interfere with the schooling of affected children. Secondary sight-threatening corneal ulceration and

scarring occurs in up to 10% of children with VKC.^{1–4} Treatment with topical corticosteroids is effective, but in countries where it is available without prescription and when used chronically without medical supervision, microbial super-infection and corticosteroid-induced glaucoma and cataract are important causes of visual loss.^{2–5} The efficiency and safety (locally and systemically) of topical ciclosporin A (CsA) as a treatment for VKC have been described in several uncontrolled and double-masked, placebo-controlled studies.^{3–6–12} However, these controlled trials were relatively small, did not compare CsA directly with corticosteroid drops and involved populations outside Africa. To further define the role of topical CsA as a treatment for VKC, we conducted a large prospective randomised double-masked, standard care controlled clinical trial in Rwanda, Central Africa. We used the null hypothesis that there would not be any clinically significant difference in efficiency at 4 weeks between CsA 2% eye-drops dissolved in olive oil vehicle and dexamethasone 0.1% drops. In addition, we examined whether there were any differences between the two treatment groups in the interval to reactivation of VKC during a period of maintenance therapy with sodium chromoglycate after the trial treatment was stopped, as well as any change in best-corrected visual acuity and any discomfort associated with therapy.

The trial was undertaken in Kabgayi Eye Unit, which is a secondary as well as a tertiary referral eye centre with over 20 000 annual outpatient attendances from all over Rwanda, of which up to 20% are for allergic conjunctivitis.

MATERIALS AND METHODS

Participants

Participants were recruited consecutively from patients attending the Kabgayi Eye Unit (Rwanda) during the dry season of July–August 2008. Inclusion criteria were: symptoms of itching for >4 weeks and a clinical diagnosis of VKC. Exclusion criteria included: age <5 years, reported pregnancy, the presence of infectious or other inflammatory ocular disease and a treatment by depot corticosteroid injection in the previous 6 months. If participants were taking topical or systemic corticosteroids, antihistamines or non-steroidal anti-inflammatory agents for VKC, a 2-week washout period was required before entering the study. A diagnosis of limbal VKC was based on the presence of limbal

papillae; a diagnosis of mixed VKC was defined as limbal papillae in combination with papillae >1 mm diameter over the upper tarsal plate; palpebral VKC with papillae confined to the conjunctiva over the upper tarsal plate was not seen. Severe VKC was defined as papillae involving 360° of the limbus.

Treatment

A clinical trial pharmacist masked to the clinical evaluation allocated the participants into two groups by block randomisation using a random-number generator sheet. Each participant then received two bottles. In one treatment group, one of the bottles contained dexamethasone 0.1% w/V (DIFAEM, Tübingen, Germany) in an aqueous solution, and the second bottle contained olive oil. In the second treatment group, one bottle contained the aqueous vehicle, and the second bottle contained CsA 2% w/V (Neoral Sandimmun 100 mg/ml, oral solution, NV Novartis Pharma SA, Vilvoorde, Belgium) dissolved in olive oil. The Local Eye Drop Production Unit of the Kabgayi Eye Unit prepared the bottles, and all drops were preserved except for CsA and olive-oil placebo. The bioavailability and stability of the CsA meant that bottles were discarded 1 month after preparation. All participants were asked to use a drop from both bottles four times daily to both eyes for 4 weeks, instilling the watery drop 5 min before the oily drop. During a 2-week visit, participants received a new pair of the trial drops. After 4 weeks, the trial medications were replaced with a single bottle of sodium chromoglycate 2% w/V (DIFAEM), which participants used four times daily in both eyes for a further 4 weeks. No other topical or systemic antiallergic medications were permitted for the 8-week duration of the trial. If there was any deterioration at 2 weeks or no improvement in symptoms and signs at 4 weeks, participants were given open-label treatment with dexamethasone 0.1% w/V four times daily as rescue medication.

Participant monitoring

Both eyes were assessed at baseline and at 2, 4 and 8 weeks. At each visit, participants were interviewed using a questionnaire based on VKC-related symptoms, best-corrected visual acuity was measured using a logMAR E Chart (Cardiff cards and Lea tests in young children) and auto-keratometry (automated portable keratometer, Nidek KM-500, Gamagori, Japan), and a slit-lamp examination was performed. We used a scoring system described by Akpek and adapted for limbal VKC to produce a composite score for both symptoms and clinical signs.¹³ The composite score for the five symptoms and the 12 signs could range from 5 to 62 (box 1) and scoring was done by the same investigator at all visits. Intraocular pressure was not recorded.

A relapse was defined as an increase in limbal follicles by at least 4 clock hours. Information on possible adverse effects was recorded, and at each follow-up visit the subjective tolerance to the trial drops was scored (box 2).

Patient compliance with the allocated treatment was monitored using a questionnaire, and the trial pharmacist compared the weight of the bottles at each visit.

The primary outcome was the change in composite score for symptoms and clinical signs at 4 weeks compared with baseline. Secondary outcomes were the change in composite score for symptoms and clinical signs at 8 weeks compared with 4 weeks, the scores for individual symptoms and signs, best-corrected visual acuity, reported side effects and tolerance to the trial drops at the 4- and 8-week visit. An analysis of composite score for symptoms and clinical signs at 2 weeks with comparison with

baseline values served to document any differences in speed of change.

Statistical analysis

The power of the study was based on the hypothesis that there would be a 50% reduction of the composite symptom and sign score of VKC with corticosteroid and a 35% reduction with CsA. This was based on the limited published data available⁹ and personal experience treating VKC in Rwanda. This indicated that we would need 182 participants per treatment arm to detect a 15% difference in the primary outcome measure between the two treatment arms of a study with 80% power and alpha-factor 0.05. We analysed the worst affected eye based on the baseline composite sign score. We used the Wilcoxon two-sample test (STATA-software V.9.2) to compare the differences in severity of the symptoms and signs in the two treatment groups. The *p* value for statistical significance was set at <0.05 for the composite score and <0.01 for the individual symptoms and signs. The principle of intention to treat analysis was used.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and the CONSORT statement, approved by the Rwandan National Ethics Committee and registered in the <http://ClinicalTrials.gov> registration system (number NCT 01211327).¹⁴ Participants or their guardians gave written informed consent. All trial medication was provided free, and participants were reimbursed for their transport to the hospital.

RESULTS

Details of enrolment, randomisation, loss to follow-up and numbers of participants analysed are shown in figure 1.

Loss to follow-up was 1.4% with no difference between the treatment groups (*p*=0.181). Characteristics of participants at the baseline examination are shown in table 1.

The intervention groups were similar with respect to age and sex distribution, disease duration and severity, eye care history, VKC subtype and VKC-related scores of symptoms and signs. At the end of the 2-week treatment period, the mean composite score had decreased significantly (*p*<0.001) from baseline by 41.2% and 46.2% for the CsA and the dexamethasone treatment group respectively, with a significant difference between the two groups (*p*=0.009).

After 4 weeks of test medication, the mean composite score for symptoms and signs had decreased significantly (*p*<0.001) further from the baseline by 47.5% and 49.9% for the CsA and dexamethasone groups respectively, the difference between groups no longer being significant (*p*=0.20) (table 2). When the composite scores for symptoms and signs were considered separately, the mean symptom scores reduced by 4.7 and 4.3 and the sign score by 7.9 and 8.9 points for the ciclosporin and dexamethasone treatment groups respectively.

History of previous eye care (*p*=0.246) or VKC severity (*p*=0.829) did not affect this difference significantly. Visual acuity improved at 4 weeks (mean log MAR −0.00, SD 0.26) and again at 8 weeks (mean log MAR −0.03, SD 0.23), without any significant differences between the two groups.

At the 8-week visit (4 weeks after the trial treatments had been stopped and replaced by sodium chromoglycate) all symptoms except photophobia had again increased with a similar deterioration in signs (table 2) but with no difference between the two treatment arms. A total of 121 participants (33.2%) had a relapse while receiving sodium chromoglycate and were treated with topical dexamethasone. There was no

Box 1 Scoring system for symptoms and clinical signs of vernal keratoconjunctivitis**Itchiness**

- 1, No desire to rub or scratch eyes
- 2, Occasional desire to rub or scratch eyes (once a week)
- 3, Frequent desire to rub or scratch eyes (once a day)
- 4, Constant desire to rub or scratch eyes

Tearing

- 1, No, normal tear production
- 2, Impression of wet eyes, without tears on the face
- 3, Intermittent tears on the face
- 4, (Nearly) constant tears on the face

Discomfort (including burning, stinging and foreign-body sensation)

- 1, No
- 2, Mild (once a week)
- 3, Moderate (once a day)
- 4, Severe (throughout the day)

Photophobia

- 1, No
- 2, Mild (light causing squeezing in bright weather)
- 3, Moderate (light causing squeezing, even in dark weather)
- 4, Severe (causing to stay indoors)
- 5, Extreme (causing to close the eyes almost all the time)

Discharge

- 1, No
- 2, Small amount of discharge
- 3, Moderate (presence of crust upon awakening)
- 4, Severe (eyelids tightly matted together upon awakening, requiring warm soaks to clean eyelids) during the day

Limbal papillae

- 0, None
- 1, ≤ 2 clock hours in total
- 2, $2 <$ clock hours in total ≤ 4
- 3, $4 <$ clock hours in total ≤ 6
- 4, $6 <$ clock hours in total ≤ 8
- 5, $8 <$ clock hours in total ≤ 10
- 6, > 10 clock hours in total

Conjunctivalisation of cornea by ≥ 2 mm

- 0, none
- 1, ≤ 2 clock hours in total
- 2, $2 <$ clock hours in total ≤ 4
- 3, $4 <$ clock hours in total ≤ 6
- 4, $6 <$ clock hours in total ≤ 8
- 5, $8 <$ clock hours in total ≤ 10
- 6, > 10 clock hours in total

Trantas dots

- 0 none
- 1 ≤ 2 clock hours in total
- 2 $2 <$ clock hours in total ≤ 4
- 3 $4 <$ clock hours in total ≤ 6
- 4 $6 <$ clock hours in total ≤ 8
- 5 $8 <$ clock hours in total ≤ 10
- 6 > 10 clock hours in total

Tarsal plate papillae

- 0, None
- 1, Papillae < 1 mm and bloodvessels visible
- 2, Papillae < 1 mm and bloodvessels obscured
- 3, Papillae ≥ 1 mm but < 3 mm
- 4, Papillae ≥ 3 mm

Box 1 Continued**Corneal defect**

- 0, None
- 1, Healed corneal shield ulcer
- 2, Corneal erosion
- 3, Active shield ulcer

Limbal cysts/pits

- 0 None
- 1 Present

Pseudomembrane

- 0 None
- 1 Present

Corneal plaque

- 0 None
- 1 Present

Astigmatism

- 0, < 1 dioptre
- 1, $1 \leq$ dioptre < 2
- 2, $2 \leq$ dioptres < 3
- 3, ≥ 3 dioptres
- 4, Examination impossible because of cloudy cornea or extreme photophobia

Conjunctival pigmentation

- 0, None
- 1, Perilimbal and ≤ 1 bulbar quadrant
- 2, Perilimbal and 1 to 3 bulbar quadrants
- 3, Perilimbal and entire interpalpebral bulbar conjunctiva

Punctate keratitis

- 0, None
- 1, One diagonal quadrant
- 2, One diagonal quadrant and central zone
- 3, Two or more diagonal quadrants

Bulbar hyperaemia

- 0, None
- 1, Vascular conjunctival injection or hyperaemia $< 360^\circ$
- 2, 360° but still white conjunctiva
- 3, 360° and obscuring normal white conjunctiva

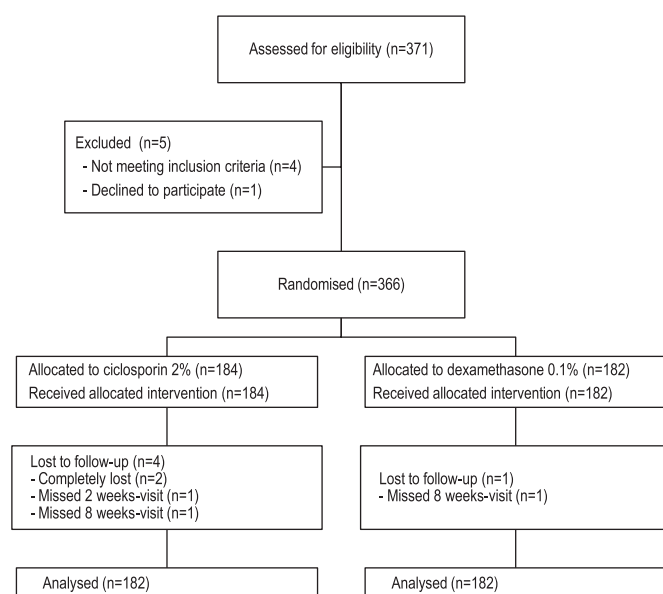
significant difference in relapse between the treatment arms ($p=0.838$).

At 4 weeks, 87.9% of participants claimed they were compliant with the treatment protocol with no difference between the treatment arms ($p=0.507$). When assessed by reduction in bottle weights, 83.2% and 62.0% of participants taking dexamethasone and its placebo were compliant at 4 weeks, compared with 56.4% and 53.4% for CsA and olive oil placebo respectively. Although the majority of participants tolerated the test medications well, the drops that contained CsA were associated with more reported discomfort than other drops ($p<0.001$), and 17.2% graded this as so severe that they

Box 2 Scoring system for tolerance of trial drops

- Grade 1: no or occasional discomfort
- Grade 2: discomfort for less than 5 min
- Grade 3: discomfort for greater than 5 min
- Grade 4: discomfort making continuation of the drop treatment difficult

Global issues

**Figure 1** Randomisation of the participants.

considered stopping treatment. In two patients, the dropper caused a corneal abrasion during application, but no other adverse events were reported during the trial. Three patients (0.8%) received rescue medication because of clinical deterioration at 2 weeks. A further 17 (4.7%) participants were put on rescue medication at the 4-week stage because there had been no

improvement during the treatment phase of the trial. The use of rescue medication tended to be more common in the CsA group compared with the dexamethasone group ($p=0.066$). Analysis excluding the participants who received rescue medication at 2 and 4 weeks found similar results for differences in composite score and visual acuity.

DISCUSSION

This study is the first large double-blind trial in Africa comparing topical dexamethasone 0.1% with CsA 2% in patients with moderate to severe limbal or mixed VKC. We found no significant difference in the effect of these two agents when we compared the composite scores for symptoms and signs measured after 4 weeks of treatment. The relapse rate after stopping treatment was similar. However, dexamethasone produced a faster effect and was better tolerated. In our study, bias was minimised by recruitment during the long dry season and low loss to follow-up.

Topical corticosteroid is considered the current standard treatment in the acute phase of VKC, but potentially sight-threatening complications are common. In regions where continuous medical supervision is not available, there is an imperative to develop a safe and effective alternative. Antihistamines and non-steroidal anti-inflammatory drugs have fewer side effects, but they do not usually control severe disease.¹⁵ Although mast-cell stabilisers have been shown to be effective in studies of VKC in Europe and North America, results from Africa have not consistently shown a benefit.^{4 6 16} Because of systemic side effects, oral corticosteroid is only used to treat potentially blinding corneal complications.⁶ Supratarsal injection of corticosteroids is very effective for temporary suppression of severe inflammation associated with VKC, but it is difficult to administer to small children without sedation, and recurrence has been reported in the majority of patients within 6 months.¹⁷ Treatment of tarsal or limbal papillae in severe VKC by cryotherapy may have only a transient response, and destruction of the limbus may exacerbate corneal stem-cell failure.^{1 2 6}

CsA is an established option for the management of VKC. It is a calcineurin inhibitor that abolishes T-cell proliferation via inhibition of CD4 T-cell receptor signal transduction and downregulation of Interleukin-2 receptor expression.¹⁸ It also inhibits apoptosis, eosinophil and mast-cell activation, and the release of IL-2, IL-1 β , IL-5 and histamine, which are thought to be important mediators of allergic inflammation.¹⁹ Topical CsA has been used in the management of several inflammatory ocular surface disorders.²⁰ Double-masked placebo-controlled studies performed in Europe and Asia report a beneficial effect of topical CsA 2% in the treatment of VKC with an aggregate reduction in scores for symptoms and signs ranging from 45 to 55% after 2 weeks.^{9 21} A study from India reported even higher success rates (66%), but with only partial data on the scores for signs and symptoms.¹² In previous placebo-controlled studies, most of the clinical improvement with the use of topical CsA was achieved in the first 2 weeks of treatment, which is consistent with our study.^{9 12 21} However, our study demonstrated that topical dexamethasone reduces signs faster than topical CsA. Studies on off-label use of topical CsA 0.05% (Restasis) have reported conflicting evidence on its beneficial effects in severe allergic conjunctivitis.^{13 22 23} Of the two studies that included cases of VKC, one small case series reported a positive effect, whereas the other (a double-masked clinical trial) failed to find any significant benefit. An Italian open trial using topical CsA dissolved in aqueous vehicle four times daily

Table 1 Characteristics and symptom and sign scores of treatment groups at baseline

Characteristic	Ciclosporin (n = 184)		Dexamethasone (n = 182)		p Value
		SD		SD	
Male	87 (47.5%)		88 (48.9%)		0.80
Disease duration of ≥ 3 years	117 (64.0%)		119 (65.0%)		0.72
No previous medical care	99 (54.7%)		97 (53.9%)		0.88
Pure limbal vernal keratoconjunctivitis	169 (91.9%)		166 (91.2%)		0.83
Severe vernal keratoconjunctivitis	65 (35.3%)		72 (39.6%)		0.40
Mean age	13.7	7.40	12.9	7.00	0.40
Mean logMAR score	-0.02	0.23	-0.03	0.23	0.42
Mean symptom score					
Itching	3.22	0.73	3.16	0.69	0.38
Tearing	2.24	0.84	2.21	0.86	0.72
Stinging	2.74	0.92	2.70	0.96	0.87
Discharge	1.84	0.87	1.81	0.79	0.98
Photophobia	2.27	0.72	2.24	0.70	0.85
Mean sign score					
Bulbar conjunctival hyperaemia	1.75	0.67	1.87	0.64	0.08
Upper tarsal conjunctival papillae	1.16	0.96	1.35	0.86	0.01
Conjunctival pigmentation	1.68	0.68	1.76	0.70	0.29
Limbal follicles	4.52	1.49	4.66	1.41	0.36
Punctate keratitis	0.90	1.21	0.87	1.18	0.89
Conjunctivalisation of cornea	0.68	1.40	0.72	1.40	0.80
Trantas dots	1.65	1.69	1.59	1.57	0.94
Corneal astigmatism	1.31	1.31	1.35	1.25	0.51
Limbal cysts	0.50	0.50	0.47	0.50	0.56
Corneal defect	0.02	0.16	0.00	0.00	0.16
Pseudomembrane	0.00	0.00	0.00	0.00	NA
Corneal plaque	0.00	0.00	0.00	0.00	NA
Mean composite symptom and sign score	26.66	7.39	26.91	6.48	0.25

Table 2 Change in mean symptom and sign scores at 4 weeks (after test medication) and at 8 weeks (after test medication and chromoglycate) in the two treatment groups, expressed as absolute values and percentages

Characteristic	Change in scores between 4 weeks and baseline					Change in scores between 8 and 4 weeks				
	Ciclosporin		Dexamethasone		p Value	Ciclosporin		Dexamethasone		p Value
	(n = 182)	%	(n = 182)	%		(n = 181)	%	(n = 181)	%	
Symptom score										
Itching	-1.59	-49.38	-1.63	-51.58	0.51	0.52	31.88	0.54	35.25	0.76
Tearing	-0.89	-39.73	-0.81	-36.65	0.47	0.24	17.94	0.30	21.58	0.40
Stinging	-1.21	-44.16	-1.23	-45.56	0.80	0.27	17.81	0.24	16.24	0.96
Discharge	-0.43	-23.37	-0.20	-11.05	0.03	0.38	26.70	0.09	5.59	0.01
Photophobia	-0.62	-27.31	-0.47	-20.98	0.23	0.07	4.23	0.01	0.57	0.25
Sign score										
Bulbar conjunctival hyperaemia	-1.33	-76.00	-1.51	-80.75	0.01	0.38	89.83	0.40	109.89	0.95
Upper tarsal conjunctival papillae	-0.42	-36.21	-0.47	-34.81	0.54	0.17	22.22	0.00	0.00	0.01
Conjunctival pigmentation	-0.18	-10.71	-0.20	-11.36	0.76	0.07	4.64	0.09	5.77	0.78
Limbal follicles	-3.59	-79.42	-4.01	-86.05	0.01	0.96	102.78	1.07	162.37	0.54
Punctate keratitis	-0.48	-53.33	-0.41	-47.13	0.48	0.13	30.02	-0.02	-4.34	0.27
Conjunctivalisation of cornea	-0.17	-25.00	-0.29	-40.28	0.21	-0.03	-5.66	-0.02	-4.73	0.91
Trantas dots	-1.38	-83.64	-1.51	-94.97	0.34	0.41	143.86	0.42	552.63	0.72
Corneal astigmatism	-0.14	-10.69	-0.23	-17.04	0.21	-0.01	-0.85	-0.01	-0.89	0.96
Limbal cysts	-0.21	-42.00	-0.30	-63.83	0.08	-0.01	-3.42	0.04	24.24	0.31
Corneal defect	-0.02	-100.00	0.02		0.05	0.00		-0.02	-95.24	0.57
Pseudomembrane	0.00		0.00			0.00		0.00		NA
Corneal plaque	0.00		0.00			0.00		0.00		NA
Composite symptom and sign score	-12.66	-47.42	-13.25	-49.26	0.20	3.29	23.65	2.95	21.85	0.45

for 4 months suggested that 1% might be the minimal effective concentration in severe VKC.⁸

Recurrence of symptoms within 2 months had been described in 75% of patients after stopping treatment with topical CsA 2%.³ Our relapse rate was lower, possibly because we started patients on sodium chromoglycate after they stopped the trial medications and also because we reported for a shorter follow-up. Future studies would be useful to investigate the minimum ciclosporin maintenance dose required to prevent recurrences. A burning sensation after administration of topical CsA has generally been reported, but this is not usually severe. It is unclear whether this discomfort was attributable to the vehicle or the CsA, but we have shown better tolerance for the olive-oil vehicle alone.^{9 12 24} Higher tolerance has been reported in trials that have used preservative-free artificial tears as vehicles for CsA and for lower CsA concentrations (0.05%).^{21 23} In our study, the tolerance of the oily drops containing CsA limited compliance and suggests that, besides a change to another vehicle, lower concentrations might improve tolerance. However, efficiency at lower concentrations for predominantly limbal forms of VKC remains to be assessed. Another limitation of topical CsA used in our study was its limited bioavailability and stability when produced locally. The €3 cost of a bottle of locally produced 5 ml CsA 2% is much less than the commercially available 0.05% preparation but still five times more expensive than dexamethasone 0.1%. In case series, the off-label use of tacrolimus ointment has controlled severe VKC, and it would be interesting to confirm an effect in a randomised clinical trial.²⁵ However, tacrolimus is more expensive than ciclosporin, and the preparation of an ointment placebo is technically more difficult than an eye-drop.

In conclusion, this study did not show any significant differences between topical CsA 2% dissolved in olive oil and topical dexamethasone 0.1% in relieving symptoms and signs of predominantly limbal VKC. Before topical CsA can be universally recommended as a safe alternative to topical corticosteroid

in developing countries, its tolerance, bioavailability and stability need to be improved.

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Competing interests None.

Patient consent Obtained.

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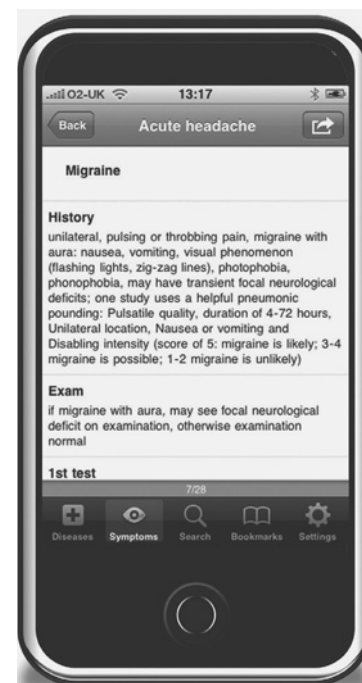
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